

discloses that Smad-1 is phosphorylated following interaction with a constitutively active ALK-1. The Examiner cites the specification, page 34, paragraph 2, "ALK-1... bind to TGF- $\beta$ 1 and activin A in the presence of their respective type II receptors, but the functional consequences of the binding of the ligands remains to be elucidated" and extrapolates from that statement to contend binding of TGF- $\beta$  to ALK-1 does not indicate that TGF- $\beta$  activates ALK-1. However, §112 requires more to support a rejection for purported non-enablement:

"[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

*In re Marzocchi*, 169 USPQ 397, 370 (CCPA 1971)

The Examiner has failed to meet his burden by failing to provide objective evidence demonstrating that one of skill in the art would doubt that TGF- $\beta$  binding to ALK-1 activates ALK-1. The Examiner has failed to cite an instance wherein TGF- $\beta$  binding to any of its cell receptors does not activate that cell receptor. Applicants respectfully request that the Examiner provide such evidence so that applicants may respond appropriately. Absent such objective evidence, applicants request, under 37 C.F.R. § 1.104(d)(2), that the Examiner provide an affidavit setting forth the facts within his personal knowledge to support his position so that applicants may respond appropriately.

One of skill in the art provided with the teachings of applicants' specification would reasonably expect that TGF- $\beta$  binds and activates ALK-1 and that the activated ALK-1 phosphorylates Smad 1. Those of skill in the art also appreciate that methods for determining the levels of Smad 1 phosphorylation in a cell sample are readily available. Thus one of skill in the art would expect that one could determine, without using undue experimentation, if a substance inhibits TGF- $\beta$ /ALK-1 induced phosphorylation of Smad-1 using the methods set forth in applicants' claims, i.e., by contacting a first sample of cells expressing ALK-1 and Smad 1 with the substance in the presence of TGF- $\beta$  and comparing the Smad 1 phosphorylation levels in the first sample of cells with a control sample of cells. A person skilled in the pertinent art, using the knowledge available and the disclosure in the application, could make and use applicants'

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invention without undue experimentation. Thus applicants have satisfied the requirements of 35 U.S.C. § 112.

In view of the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under § 112, first paragraph.

Claim 52 stands rejected under 35 U.S.C. § 112, first paragraph for purported lack of enablement. In particular, the Examiner contends that if the ALK-1 is a constitutive ALK-1 then it would phosphorylate Smad-1 regardless of whether TGF- $\beta$  was present or not. Thus one could not determine if a substance inhibited the TGF- $\beta$ /Alk-1 induced phosphorylation of Smad-1. Applicants have cancelled claim 52 without prejudice and expressly reserving the right to pursue the subject matter of claim 52 in one or more subsequent applications. In view of this cancellation, this rejection is no longer applicable.

In view of the foregoing remarks and amendments to the claims applicants respectfully request that the Examiner withdraw the rejections and allow the claims.

The Commissioner is hereby authorized to deduct any missing or insufficient fees related to the filing of this document from Deposit Account No. 06-2375.

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Respectfully submitted,

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